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Alteration of brain regional homogeneity of monkeys with spinal cord injury: A longitudinal resting-state functional magnetic resonance imaging study

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ABSTRACT

Purpose: To investigate the longitudinal brain regional homogeneity (ReHo) changes in nonhuman primate after spinal cord injury (SCI) by resting-state functional magnetic resonance imaging (fMRI).
Methods: Three adult female rhesus monkeys underwent unilateral thoracic cord injury. A resting-state fMRI examination was performed in the healthy stage and 4, 8, and 12 weeks after the injury. The ReHo value of each voxel in the monkey brain was calculated and compared between pre- and post-SCI monkeys with paired t test. The regions of interest (ROIs) in the significantly changed ReHo regions were set. The correlations between the ReHo change and the time after injury were also determined.
Results: Compared with those in healthy period, the ReHo values of the left premotor cortex and the anterior cingulate cortex (ACC) in post-SCI rhesus monkeys significantly increased in 4-week follow-up examinations. The ReHo values of posterior cingulate cortex, left precuneus, left temporal parietooccipital area, and bilateral superior parietal lobules decreased at 8-week follow-up examinations. In 12-week follow-up examinations, the ReHo values of the left postcentral gyrus, right caudate nucleus, and superior temporal gyrus increased. Correlation analysis showed positive correlations between left ACC and the postoperative time.
Conclusion: SCI can change the regional synchronism of brain activity in sensorimotor system and the default mode network. These findings may help us to understand the potential pathophysiological changes in the central nervous system after SCI.

1. Introduction

Traumatic spinal cord injury (SCI) can destroy ascending sensory and descending motor conductive nerve fibers in the spinal cord. Owing to the lack of axonal regeneration ability in the adult central nervous system (CNS), SCI usually leads to permanent loss of sensory and voluntary motor functions and becomes a serious and incurable disease of the nervous system. The destruction of axonal nerve conductions caused by SCI adjusts the sensory and motor information transfer between the spinal cord and brain and induces changes of structure and function in the nervous system [1,2]. Functional magnetic resonance imaging (fMRI) provides an important noninvasive detection method to diagnose and assess the effect of SCI on sensory and motor functions. Many previous fMRI studies have reported the activation of sensory cortex [3–5] and motor cortex [6–8] induced by tasks expanded to the adjacent area after SCI. Although many task-associated fMRI studies have proved the changes of cerebral cortical activation induced by SCI, changes in spontaneous brain neuronal activations under the resting state are few and remain still unclear.

As a branch of brain functional imaging, resting-state fMRI reflects the neuronal spontaneous activities in various brain regions [9] and the intrinsic functional organization [10] by detecting the low-frequency fluctuation (LFF) of blood oxygenation level-dependent (BOLD) contrast signal. The LFF of BOLD signal at resting state was first found in the human motor cortex [9] and subsequently extended to primates [11–13] and rodents [14–17]. Although resting-state fMRI has been widely used to study cranial nerve system disease [18–21], studies on SCI are few. Choe et al. [22] reported that SCI enhanced the functional connection between sensorimotor cortex and visual cortex, which demonstrated that the pathological changes of SCI caused the change of brain at resting state. Noor et al. [23] demonstrated SCI-induced changes of default

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mode network (DMN) and fronto-lateral network by comparing SCI patients with different degrees of paralysis. Hou et al. [24] showed that acute SCI patients had abnormal amplitude of LFF and functional connections in the multiple brain regions, and these alterations had relationship with clinical motor scores. Our recent study [25] revealed that SCI caused abnormal LFF changes that appear in DMN, superior parietal lobule (SPL), thalamus, and cerebellum regions. These studies have shown that SCI can change the brain functional connection between brain regions and the LFF magnitude in brain regions. However, the effect of SCI on regional collaborative activity has not been reported.

Regional homogeneity (ReHo) is a new method to assess the local coherency of spontaneous LFF of BOLD signal at resting state. This method uses Kendall's coefficient of concordance (KCC) [26] to calculate the time series similarity between a given voxel and adjacent voxels to analyze the coherence of regional brain activities [27]. Unlike the functional connections and LFF amplitude, ReHo does not focus on the intensities of regional BOLD signal [28] but reflects the degree of coherence within local brain activities. Although the neural mechanism underlying ReHo is not well understood, the method has been used to assess the resting-state functional modulations caused by many cranial diseases, including Alzheimer's disease [29], Parkinson's disease [30], autism [31], and depression [32], and proved to be helpful to diagnose the alteration of synchronization caused by disease.

We hypothesized that the abnormally local collaborative activity in some components of the sensorimotor cortex and the DMN may be triggered during the development of SCI. To validate this hypothesis, the changes of resting-state ReHo in three female rhesus monkeys were longitudinally assessed at healthy period and 4, 8, and 12 weeks after thoracic spinal cord hemisection to evaluate the evolution of functional status after SCI.

2. Methods

2.1. Animal preparation

Three adult female rhesus monkeys (weight: 5.53 ± 0.42 kg; age: 5.72 ± 0.21 years old) were used in this study. The experiment was approved by the Animal Ethics Committee of the Capital Medical University. Under an operation microscope, a right hemisected injury was performed at the T7–9 level of the thoracic spine (approximately T10–12 level of the spinal cord) after laminectomy. The midline posterior vein of the spinal cord was identified as an anatomic landmark, and lesion was started 0.5 mm lateral to the spinal cord midline. A segment of tissue of 10 mm length (in the rostrocaudal position) and 2–3 mm width (in the left–right direction) was excised from spinal cord by using microscissors. The motor function of the right hind limb was immediately lost but the bowel and the bladder functions were retained after the lesion surgery. All monkeys were individually housed in a temperature- and humidity-controlled chamber. Food and water can be accessed ad libitum, and fresh fruits were provided daily. Resting-state fMRI examination was performed in the healthy stage and 4, 8, and 12 weeks postoperative. These time points were selected base on the premise of the stable physical condition of the SCI animals. Each rhesus monkey was given ketamine hydrochloric acid solution (10 mg/kg, i.m.) and atropine sulfate injection (0.05 mg/kg, i.m.) before scanning to induce anesthesia and to decrease bronchial and salivary secretions. Anesthesia was maintained during the scan by continuous administration of propofol (0.25 mg/kg/min, i.v.). Corneal reflex, somatic movement, O_2 saturation, heart rate, respiration rate and body temperature were monitored periodically during the MRI experiments. The level of anesthesia was determined with the following reactions as the standard: (i) before scanning, corneal reflex disappeared and no somatic movement when the toes were pinched; (ii) during scanning, heart rate was kept higher than 70 times/min, and respiration rate was higher than 20 times/min [12].

2.2. Data acquisition

All data were acquired by a custom-made four-channel primate head transmitter receiver coil on a 3 T Siemens MR system (Siemens, Erlangen, Germany). Functional data scanning was obtained with the following gradient echo-echo planar imaging sequence: TR/TE = 2000 ms/30 ms, field of view = 128 mm × 128 mm, matrix = 64 × 64, slice thickness = 2 mm, and flip angle = 90°. Twenty-five consecutive slices of the axial images covered the entire brain. Each scan period was approximately 4 min and 120 volumes were obtained. Structural data were acquired by the following 3D magnetization prepared rapid acquisition gradient echo sequence: TR/TE = 1520 ms/4.42 ms, flip angle = 15°, and TI = 520 ms. Structural data had the same centering as functional data. A total of 180 consecutive slices covered the entire brain, with an isotropic voxel size of 0.5 mm^3.

2.3. Data processing

SPM8 (http://www.fil.ion.ucl.ac.uk/spm), Resting-state fMRI Data Analysis Toolkit (REST V1.8, http://www.restfmir.net), and Data Processing Assistant for Resting-state fMRI (DPARSFA V2.3) were used for data processing. The preprocessing included compensation time delay, head motion correction (six-parameter rigid body transformation), and spatial normalization. Head motion correction was used to evaluate whether the head movement met the requirements of data acquisition process (displacement <1 mm, rotation <1°). After head motion correction, the images were spatially normalized to INIA 19 Primate Brain Atlas [33], and then the coordinates were transformed to the Montreal Neurological Institute space. The first 10 volumes of resting-state data of each animal were discarded to avoid the possible instability of the initial MRI signal. Low-frequency drifts and high-frequency physiological noise were removed using a temporal band-pass filter (0.01 Hz to 0.08 Hz). ReHo values of all voxels in the entire brain were calculated. Time course KCC values between the given voxels and the nearest 26 neighbor voxels (a total of 27 voxels) were calculated to extract the ReHo value of each voxel. The formula was as follows [27]:

$$W = \frac{\sum (Ri)^2 - n(\overline{R})^2}{\left(\frac{1}{12}\right)K^2(n^3 - n)},$$

where W is the KCC for a given voxel, which ranges from 0 to 1; Ri is the sum rank of the ith time point; $\overline{R} = {}^{(n+1)K}/_2$ is the mean of Ris; K is the number of time series within a measured cluster ($K = 27$); and n is the number of ranks ($n = 110$ time points). To decrease the effect of individual variability, the ReHo value of each animal was divided by its own mean ReHo of the entire brain to standardize [34]. Finally, a 3 mm full-width-at-half-maximum Gaussian kernel was used for spatial smoothing.

2.4. Statistical analysis

REST V1.8 was used to analyze the fMRI data statistically. To explore the effect of SCI on the brain function of animals, we used paired t-test to detect the differences between healthy ReHo value and postoperative ReHo value in a voxel-by-voxel manner (healthy period vs. 4 weeks post-SCI; healthy period vs. 8 weeks post-SCI; healthy period vs. 12 weeks post-SCI). The significant level was set to $P < 0.05$. Gaussian random field (GRF) theory was used for multiple comparison correction. The cluster size was >40 mm^3 (5 voxels). Significantly altered ReHo regions in the pre- and

post-SCI comparisons were selected. With the peak voxel as the center, the spherical region of interest (ROI) with a radius of 4 mm was drawn. The average ReHo values at different time points were then extracted from the ROIs of each monkey. Using SPSS 17.0 (SPSS Inc. Chicago, IL), Spearman correlation analysis was used to calculate the relationship between the mean ReHo values and the discrete time after SCI. The significant level was set to $P < 0.05$. All data were given in the form of mean ± standard deviation.

3. Results

Three animals lost motor function in the right hind limb after SCI, but the motor functions of the other three intact limbs were preserved to maintain their daily activities. All data showed the displacement/rotation of animal head in *X*, *Y*, and *Z* directions <1 mm/1°. The head movements were in line with the requirements.

Fig. 1 and Fig. S1 (Supplementary Fig. 1) show the result of the paired t-test. Compared with the healthy stage, the ReHo values of the left premotor cortex (PMC) (BA6) and the left anterior cingulate cortex (ACC) (BA24) significantly increased 4 weeks after SCI. ReHo values in many brain regions, including the posterior cingulate cortex (PCC) (BA23/31), left precuneus (PCu), left temporal parietooccipital area (TPO), and bilateral SPL (BA5), significantly decreased at 8 weeks post-SCI. At 12 weeks post-SCI, animals showed pronounced increase in ReHo values in the left medial postcentral gyrus (PoCG) (BA1/2), right caudate nucleus (Cd), and right superior temporal gyrus (STG). Table 1 shows the detailed information for the brain regions with significant ReHo difference at each time point.

The region in which the significant difference of ReHo appeared was defined as ROI. A total of 10 ROIs were defined, namely, left PMC, left ACC, left PCu, left TPO, left SPL, left PoCG, right SPL, right Cd, right STG, and PCC. For all animals at different time points, the ReHo values of all ROI voxels were averaged and extracted for correlation analysis. A significant positive correlation was observed between the left ACC and the time after SCI ($r = 0.626$, $P = 0.029$) (Fig. 2A). We also observed a closely significant correlation between the right Cd and the time after SCI ($r = 0.540$, $P = 0.070$) (Fig. 2B). No significant correlations were observed between other ROIs and time after SCI ($P > 0.05$).

4. Discussion

In this study, we conducted a longitudinal assessment on ReHo changes of brains in three rhesus monkeys in the healthy period and 4, 8, and 12 weeks after SCI by resting-state fMRI. We also explored the relationship between the change of ReHo value and time after SCI. Results showed that compared with that at healthy stage, the animals displayed a diffused abnormal homogeneity at all postoperative time points. These results suggested that SCI affected the synchronization of local brain activity in multiple regions in primates. Furthermore, the correlation analysis result between ReHo value and time points showed continuous modulation on left ACC caused by thoracic spinal cord hemi-injury. Our findings may provide evidence to prove that SCI can change the homogeneity of brain neuronal activity.

BOLD signal at resting state may reflect the spontaneous activity of neurons [9]; therefore, the ReHo value derived from BOLD signal may be a useful marker to show the neuronal function within the local regions [35]. In this study, we found that compared with that in healthy period, the ReHo values in the left PMC (BA6) and ACC (BA24) significantly increased at 4 weeks after SCI. Previous studies have reported that a motor task would increase the activation of PMC after SCI [36–38]. Since SCI damaged the control of the left motor cortex to the right hind limb, the enhanced ReHo value in the left PMC may represent the integration of local functional unit to complete the processing of movement function. ACC is a component part of DMN and is involved in many brain functions. A previous study [39] suggested that ACC is responsible for the integration of pain experience, negative emotion, and related cognitive control. In our study, the abnormally enhanced synchronization of left ACC activity may be related to many factors, and the potential mechanisms underlying this alteration are still unclear.

The ReHo value in widespread brain regions of a rhesus monkey, including PCC, left PCu, left TPO, and bilateral SPLs, significantly decreased at 8 weeks postoperative. These brain regions can be divided into two categories: the region involved into the sensory information processing (bilateral SPLs) and the component of DMN (PCC, PCu, and TPO) [13]. SPL mainly receives the fibers derived from the adjacent primary somatosensory cortex (S1) and is related to the integration of common sense, tactile, and visual information [40,41]. The decrease in the ReHo value of the right SPL may be attributed to the fact that the right hemi-transection of the thoracic spinal cord obstructed the input of sensory information in the right pathway. On the contrary, the reduction of ReHo value in the left SPL may be partially attributed to local function disintegration caused by the regional function decrease of contralateral (right) SPL [42]. Meanwhile, the reduction of brain activity consistency in network node showed that DMN was in abnormal state after SCI, which was consistent with previous studies [23,25]. PCC/PCu is considered to be the core node of DMN, which receives signals from the frontal, parietal, and temporal lobes [43,13], and plays a pivotal role in monitoring the surrounding environment [44] and maintaining self-consciousness and cognitive-affective interaction [45]. The appearance of decomposition synchronization of PCC/PCu local activity after SCI may be due to the absence of its own information or abnormality of parietal cortex areas activity caused by the reduction of synchronization of SPL. We also observed that the ReHo value of TPO decreased, which may be caused by the abnormal activity of PCC/PCu via afferent and efferent connections among three nodes [46,13].

At 12 weeks post-SCI, the ReHo values significantly increased in the left medial PoCG, right Cd, and STG regions. The left medial PoCG was a cortical projection representation of the sensory information of the right hind limb [47]. The significant enhancement of the ReHo value suggested that the synchronization of cortical activity in the region was higher than that at the healthy period; this finding suggests that the region may be in an abnormal functional status. Previous studies [48,49] have exhibited the SCI-induced hypersensitivity of body on temperature and mechanical stimulation. They have also shown that increased activation in the S1 cortex contralateral to injury is one of the main characteristics of neuropathic pain in rat after SCI [50]. The extraordinarily high synchronization of regional activities in hind limb cortical projection area observed in this study reflected the high degree of functional integration of local cortical areas [51], which may be the physiological basis of hypersensitivity. The right Cd had an important contribution to maintain the posture of trunk and limbs, which controlled the speed and accuracy of motion [52]. STG was the motion imitation area and was involved in the processing of motion information [53,54]. A previous study [36] has reported increased STG activation when SCI patients performed an action. For these reasons, the current study observed that the significantly increased ReHo in Cd and STG may be associated with the changes of motor functions.

Though part of limbs affected by SCI, functional circuitry [55,1], neuronal structure [56,2] and neuronal excitability [57,58] were notably changed within the spinal cord and brain level. For this reason, we have observed diffused abnormal homogeneity in multiple brain regions. However, compared to the healthy stage, ReHo values in the significantly changed areas showed mainly increase (4 weeks)–decrease (8 weeks)–increase (12 weeks)

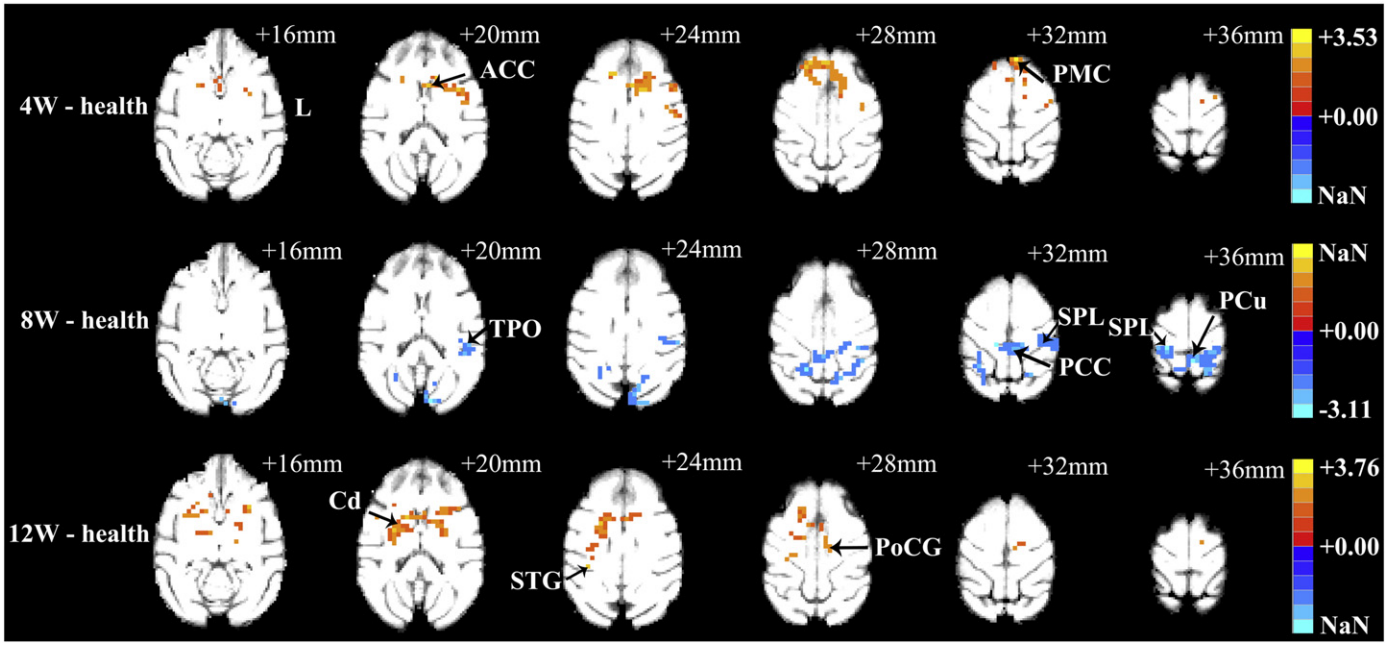

Fig. 1. Group analysis results of ReHo values at different time points after SCI compared with those in healthy period. Statistical map shows the area where ReHo values of post-SCI animals were significantly higher (red) and lower (blue) than those of the healthy stage ($P < 0.05$ with GRF for multiple comparison correction, cluster size >40 mm^3). The color scale indicates t values. Montreal Neurological Institute coordinates are given in the upper right corner. L: left; W: weeks; ACC: anterior cingulate cortex; PMC: premotor cortex; TPO: temporal parietooccipital area; SPL: superior parietal lobule; PCC: posterior cingulate cortex; PCu: precuneus; Cd: caudate; STG: superior temporal gyrus; PoCG: postcentral gyrus; GRF: Gaussian random field theory.

Table 1
Detailed information of clusters showing significant ReHo difference of the animals after SCI in paired comparison with pre-SCI ($P < 0.05$ with GRF for multiple comparison correction, cluster volume > 40 mm^3).

Time post SCI	Brain regions	PV_X	PV_Y	PV_Z	V (mm^3)	t value
4 W	Left PMC	−2	36	32	200	+3.81
	Left ACC	−4	26	22	192	+4.23
8 W	Left PCu	−2	−4	36	448	−3.22
	Left SPL	−18	8	34	184	−2.66
	PCC	0	4	34	144	−3.43
	Right SPL	12	0	34	136	−3.14
	Left TPO	−24	4	22	96	−3.22
12 W	Right Cd	6	24	22	2040	+4.51
	Left PoCG	−6	12	30	128	+2.84
	Right STG	16	2	24	72	+3.15

W: weeks; PMC: premotor cortex; ACC: anterior cingulate cortex; PCu: precuneus; SPL: superior parietal lobule; PCC: posterior cingulate cortex; TPO: temporal parietooccipital area; Cd: caudate; PoCG: postcentral gyrus; STG: superior temporal gyrus; GRF: Gaussian random field theory; PV: peak voxel; X, Y, Z: Montreal Neurological Institute coordinates; V: Cluster volume (one voxel = 2.0 mm × 2.0 mm × 2.0 mm); t: t values from a paired two tailed t-test of the statistical different clusters; a positive t value means increased ReHo values in SCI animals.

alterations after SCI. This phenomenon may be attributed to the fact that the initial lesion was located far from the brain, i.e., at the thoracic spinal T10–12 segments. The original damage cannot immediately alter the anatomical structures of the brain but gradually affects the volume of brain gray/white matters via the anatomical connection in subsequent time [4]. Therefore, the change in brain functional state after SCI suffered from the common modulation of its own properties, pathological process, CNS plasticity, and other factors, thereby showing variance mixture effect. Nevertheless, we still observed that the left ACC was significantly correlated with the postoperative time, which may show the change of senior emotional activity after SCI. Unlike the significant increase of ReHo value in motor relevant regions at 4 and 12 weeks, the ReHo value of sensory information processing and DMN-related regions obviously decreased in 8 weeks. This result may show the modulation of sensory system and DMN, which was guided by lack of sense and reached the maximum at 8 weeks after SCI.

A previous study has reported that anesthesia with propofol will influence the functional connectivity of inter-cortexes [59] and between cortex and subcortex [60], as well as may weaken the spontaneous neuronal activity in specific brain regions [25]. To assess the influence of anesthesia, two healthy monkeys were suffered an additional MRI examine. Functional data for each animal were acquired at two time points (interval: 18 min) and were analyzed in the same way. ReHo values in the 10 ROIs (mentioned in the Results) were extracted (Supplementary Table 1). The paired t-test results showed no significant changes in ReHo values between two time points (in the 10 ROIs, $P = 0.977$; in the whole brain, $P > 0.05$ with GRF for multiple comparison correction and cluster size >40 mm^3, Fig. S2). These results show that anesthesia with propofol might have affected the synchronization of local brain spontaneous activity less because ReHo does not focus on the intensities of regional BOLD signal [28].

Our study has some limitations. First, using hemisected SCI animal model can avoid the effect of different SCI conditions (damage location and severity) on the results. However, accurately predicting the extent of plasticity in CNS after SCI is difficult. Consequently, our study could not distinguish the separate contributions between SCI and the plasticity to ReHo. Second, no differentiation between the representation of the right hind limb and other sensorimotor cortex was observed; this may be due to the sparse time points or the partial SCI animal model. Finally, this study is limited by the small sample size; thus, statistical analysis results may have limitations. Further study with large samples is necessary.

5. Conclusion

Although varied homogeneity was observed in multiple brain regions, this research suggested that SCI will have a continuing effect on the synchronization of brain regional areas, thereby leading to the alterations of functional activity coherence in the brain sensorimotor system and the DMN node. This finding suggested that the different changes of cerebral function states in the sensory and motor system are induced by a series of potential pathophysiological processes after SCI.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.mri.2015.06.011.

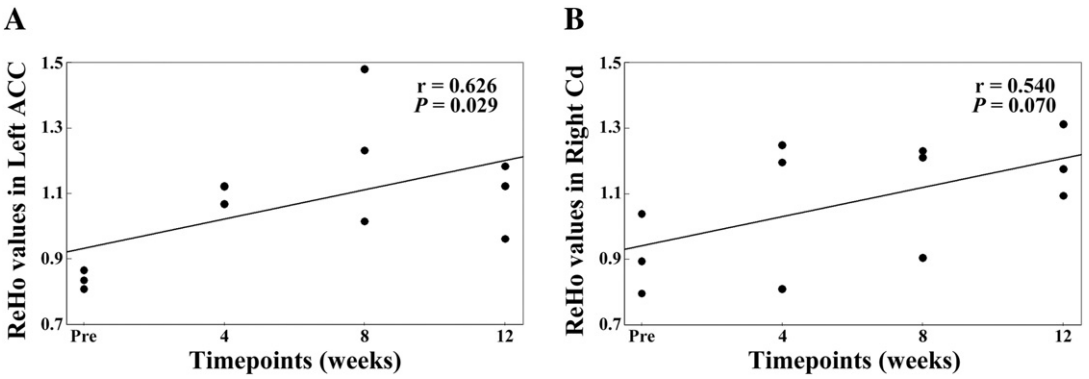

Fig. 2. Scatter plot diagrams illustrated the relationship between the ReHo value of the brain regions and the time after SCI. (A) A significant positive correlation was found between the ReHo of the left ACC and the time after SCI. (B) A closely significant correlation was observed between the ReHo of the right Cd and the time after SCI. The straight line in the figure is the linear regression line to match the data. ACC: anterior cingulate cortex; Cd: caudate.

Conflicts of interest

All authors declare that they have no conflict of interests.

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